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Attorney Docket No. 15966-557 CIP1 (CURA-57 CIP1)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

Art Unit:	1647
Examiner:	Christine J. Saoud
Appellants:	Jeffers *et al.*
Serial No.:	09/609,543
Filed:	July 3, 2000
For:	NOVEL FIBROBLAST GROWTH FACTOR AND NUCLEIC ACIDS ENCODING SAME

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BRIEF ON APPEAL

Sir:

Appellants file this Appeal Brief with the Board of Patent Appeals and Interferences (i.e., the "Board"), in triplicate, pursuant to 37 C.F.R. § 1.192(a), in support of their Notice of Appeal, dated April 14, 2003. A one-month's extension of time is believed necessary and accompanies this Appeal Brief. In addition, a check in the amount of $160.00 (Check No. 16667) is enclosed to cover the fee for filing a brief in support of an appeal required under 37 C.F.R. § 1.17(c).

The Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to Deposit Account No. 50-0311, Reference 15966-557 CIP1 (Cura-57 CIP1).

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This Brief has the following Exhibits:

Exhbit 1: Jeffers, *et al*, 2002 *Gastroenterology* 123: 1151-1162; and

Exhibit 2: Press Release announcing the FDA approval of CuraGen's (the assignee of this application) Investigational New Drug application to initiate human clinical trials using FGF-CX to treat oral mucositis.

LIST OF CASES CITED

In re Gottlieb 328 F.2d 1016 (CCPA)

In re Brana 51 F.3d 1560 (Fed.Cir. 1995)

In re Jolles, 628 F.2d 1322 (C.C.P.A. 1980)

Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555 (Fed. Cir. 1992)

REAL PARTY IN INTEREST

The real party in interest in this Appeal is CuraGen Corporation of New Haven, Connecticut, the sole assignee of each inventor's complete interest to all inventions described in the present application.

RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any other appeal or interference proceedings that will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

Pending claims 1, 5, 41, 46, 63 and 64, as set forth in the Appendix, are before the Board. Each of these claims has been given a Final Rejection by the Examiner.

STATUS OF AMENDMENTS

Appellants have brought this action before the Board in lieu of the position taken by the Examiner in the Examiner's Office Action of December 12, 2002 in which the claims now pending before the Board were finally rejected. The pending claims stand as amended on October 7, 2002, in response to the April 17, 2002, Examiner's non-final office action.

Prior to submitting this Brief on Appeal to the Board, and in response to the Examiner's Action of December 12, 2002, Appellants filed a Response and Amendment with the Examiner on February 6, 2003 in which they canceled claims drawn to non-elected subject matter. An Examiner's Advisory Action, mailed on March 4, 2003 ("First Advisory Action"), indicated that the Response and Amendment would be entered for purposes of Appeal, but that it did not place the application in condition for allowance because the asserted use of "promoting growth of cells in the lining of the GI tract in order to treat intestinal inflammation and ulcers" is not specifically recited in the specification as filed because it was but one in a list of unrelated uses.

Subsequently, Appellants filed a Supplemental Response requesting reconsideration, together with their Notice of Appeal, on April 14, 2003. In a Supplemental Advisory Action mailed on May 14, 2003 ("Supplemental Advisory Action"), the Examiner indicated that the April 14, 2003, Supplemental Response was entered but did not place the application in condition for allowance because: "[I]t does not support a substantial utility of the claimed invention as originally filed. Use for treatment of ulcers was not substantial at the time it was filed."

SUMMARY OF INVENTION

The application now before the Board is a continuation-in-part of co-pending United States Patent Application Serial No. 09/494,585, filed January 31, 2000, which in turn claims priority from the filing date of United States Patent Application Serial No. 60/145,899, of July 27, 1999, now abandoned. The subject matter of the application before the Board, namely an

isolated FGF-CX polypeptide of SEQ ID NO:2, has been disclosed and described since the January 31, 2000 filing date.

The claims of the present application are directed to a novel polypeptide having homology to members of the Fibroblast Growth Factor (FGF) family of proteins. Specifically, these peptides are named Fibroblast Grown Factor-CX (i.e., "FGF-CX"). An example of a specific FGF-CX polypeptide, and the FGF-CX polypeptide that is specifically named in the claims involved in this appeal, is the polypeptide comprising the amino acid sequence of SEQ ID NO:2 as defined within the claims and specification of the application now before the Board in this matter. As fully disclosed and described within the above-captioned application, the working examples on page 101, line 12, to page 104, line 18, clearly demonstrate that an FGF-CX protein as claimed is useful in stimulating cell growth, including the growth of fibroblasts, and is a therapeutic target having a promoting role in tumor progression.

ISSUES BEFORE THE BOARD

Rejection Under 35 U.S.C. § 101

Whether Claims 1, 5, 41, 46, 63 and 64 fail to meet the specific, substantial, or credible utility requirement under 35 U.S.C. § 101.

Rejections Under 35 U.S.C. § 112 ¶ 1

Whether Claims 1, 5, 41, 46, 63 and 64 fail to meet the enablement requirement under 35 U.S.C. § 112, ¶ 1, given the rejection under 35 U.S.C. §101.

GROUPING OF CLAIMS

The pending claims all recite an isolated polypeptide comprising an amino acid sequence shown in SEQ ID NO:2. To the extent that the Examiner has applied a utility

rejection to this FGF-CX polypeptide of SEQ ID NO:2, these claims stand or fall together, as discussed below.

ARGUMENTS

The pending claims were entered in Appellants' October 7, 2002 response to the April 17, 2002, non-final Office Action. The only issues remaining are whether the Appellants had met their burden of showing specific, substantial and credible utility at the time of filing the application.

The Claimed Invention

The invention described and claimed in the application before the Board relates to an isolated polypeptide comprising an amino acid sequence shown in SEQ ID NO:2. This polypeptide is alternatively referred to throughout the specification by the term "FGF-CX" or "FGF-20X". The polypeptide is also specifically referred to in each of the claims before the Board by its specific ID number.

Appellants have organized this Brief on Appeal first to provide reasons why the Examiner's rejection under 35 U.S.C. § 101 is Improper; and second to provide reasons why the Examiner's rejection under 35 U.S.C. § 112 ¶ 1 is Improper.

1. Appellants believe that the Examiner's rejection of Claims 1, 5, 41, 46, 63 and 64 under 35 U.S.C. § 101 is improper for the following reasons:

Claims 1, 5, 41, 46, 63 and 64 have been finally rejected as lacking utility "because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility" (page 3 of the December 12, 2002 Examiner's Action). In the First Advisory Action, the Examiner contends that, because multiple utilities are recited in the specification, no "specific" utility has been recited. Appellants disagree.

On pages 3 and 4 of the December 12, 2000 Final Office Action, the Examiner had set forth multiple reasons for rejecting Appellants' showing of specific examples of utility contained throughout the specification as initially filed.

The record is clear that the specification makes a specific assertion of utility for the claimed invention, i.e., the polypeptide comprising the novel FGF-CX protein of SEQ ID NO:2 to which each of the claims before the Examiner and the Board is limited.

The proteins of this invention may be used to stimulate cell growth, including especially growth of fibroblasts and epithelial cells in the linings of the gastrointestinal tract. Stimulation of cell growth is described in the specification as filed on pages 102 to 104, line 18. The Board's attention is directed, for example, to Example 10 on page 103 where it is expressly stated that the purpose of Example 10 was "To determine if recombinant FGF-CX induces cell proliferation...", and "It was found that FGF-CX induces about a 3-fold increase in cell number relative to control protein in this assay (Fig. 17)". Example 10 concludes with the statement: "These results show that FGF-CX acts as a growth factor and suggest that recombinant FGF-CX mediates the morphological transformation of NIH 3T3 cells". Appellants believe that this teaching is sufficient to provide an assertion of utility for the present invention, that the assertion identifies a specific utility which would be considered by those skilled in the art to be a substantial utility, and furthermore that the assertion of this specific and substantial utility is also credible. As such, any rejection under Sections 101 and 112, paragraph 1 of the patent code cannot be maintained. Accordingly, Appellants request the Board to find that the specification expressly provides for a specific, substantial credible utility, and to withdraw the rejection.

In addition, Appellants assert that the polypeptide comprising SEQ ID NO:2 has a credible utility in promoting growth of cells in the lining of the gastrointestinal tract in order to treat intestinal inflammation and ulcers. This demonstrated utility was discussed during a telephone conference with the Examiner on January 9, 2003. This activity is disclosed in the specification as it was originally filed (at page 4, lines 21 to 27, and page 68, lines 24 to 27, for example) and has now been published by Jeffers, *et al*, in *Gastroenterology* 123:1151-1162 (2002) which was filed with the Examiner together with the Response mailed February 6, 2003, as Appendix A. Appellants are also providing the Board with a courtesy copy of this reference as Exhibit 1 attached to this Brief on Appeal. As discussed with the

Examiner during a January 9, 2003 telephonic conference, this utility of treating ulcers and cells lining the gastrointestinal tract was disclosed in the specification as filed at various other locations, including the following:

> "The invention includes a method of promoting growth of cells in a subject ... In some embodiments, the cells whose growth is to be promoted may be ... cells in the lining of the gastrointestinal tract." See page 5, lines 15 to 21.
>
> "FGF-CX can also be used to stimulate fibroblasts (for accelerating healing of ... ulcers)". See page 77, lines 29 and 30.
>
> "The proteins of the invention may be used to stimulate cell growth and cell proliferation in conditions in which such growth would be favorable. An example would be [in] ... linings of the gastrointestinal tract." See page 77, lines 26 to 29.

Appellants also describe this utility in the "Uses and Methods of the Invention" section covering pages 67 to 90 of the specification as initially filed. Particularly in the "Diagnostic Assays" subsection, extending from page 76 to 79 of the specification, Applicants provide details of stimulation of epithelial cells, glial cells, and cells found in the lining of the gastrointestinal tract. See, *e.g.*, page 76, line 29 to page 77, lines 9, and page 77, lines 26 to 31.

In the Advisory Action, the Examiner asserted that Appellants' response filed February 6, 2003, did not place the application in condition for allowance because the "asserted use of 'promoting growth of cells in the lining of the GI tract in order to treat intestinal inflammation and ulcers' is not specifically recited in the specification as filed because *it is but one in a list of unrelated uses*" (emphasis added). Appellants disagree and they request the Board to find in their favor. The fact that multiple utilities are recited in the specification does not mean that there is a lack of a specific, substantial and credible utility. As the MPEP makes clear, "[i]t is common and sensible for an applicant to identify several specific utilities for an invention." See MPEP § 2107.01. The case law is also clear. In re Gottlieb 328 F.2d 1016 (CCPA), is particularly relevant. In Gottlieb, multiple utilities were

disclosed. The Court held that one specific utility was sufficient to meet the utility requirement (328 F.2d at 1018). That is all that is required here also. *See a*lso In re Brana 51 F.3d 1560 (Fed.Cir. 1995).

Appellants have submitted unequivocal evidence of record that confirms that the proteins claimed in the invention have precisely this activity. As stated above, Appellants previously made of record Appellants' published work demonstrating that administration of FGF-CX protein in fact "enhances the growth of intestinal fibroblasts." *See* Jeffers *et al.* (citing Abstract), (Exhibit 1).

In addition, Appellants submitted a Press Release announcing the FDA approval of CuraGen's (the assignee of this application) Investigational New Drug application to initiate human clinical trials using FGF-CX to treat oral mucositis – oral mucositis is a side effect of chemotherapy and radiotherapy resulting in the degradation of mucosal tissue that can range from redness and irritation to severe ulcerations of the mouth and throat (a courtesy copy is attached as Exhibit 2). In this trial, FGF-CX is being tested for its ability to stimulate cell proliferation (specifically proliferation of fibroblasts and epithelial cells) and to counteract toxic side effects of chemotherapeutic and radiotherapeutic agents in the throat and mouth (*i.e.*, linings of the gastrointestinal tract), precisely as recited in the specification. Appellants believe that the Board must agree that this is more than is required to prove an overabundance of utility in front of the United States Patent and Trademark Office.

For the record, Appellants note that utility is also supported by the structural similarity of FGF-CX with other known members of the FGF family and specifically contains a conserved family domain and hydrophobic transport domain (see page 91, lines 3 to 7 of the specification as filed). In addition, the claimed FGF-CX polypeptide has a biological activity similar to a structurally related fibroblast growth factor-9 (FGF-9) compound already known and tested in the art for activation/proliferation of glial cells and fibroblasts (see pages 76 and 77 of the specification as filed along with FIGS. 4 and 5). Other known FGFs have been shown to be useful in the stimulation of wound healing (see, for example, United States Patent 5,804,213). In addition, case law holds as valid a utility for claimed compounds based on

structural features similar to the facts in the instant application, for example, the Court finding utility for claimed compounds having close structural relationship to other compounds known to be useful in cancer therapy in In re Jolles, 628 F.2d 1322 (CCPA 1980); or stating that although it may be true that minor changes in chemical compounds can radically alter their effects, evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility in In re Brana 51 F.3d 1560 (Fed. Cir. 1995). Thus, the particular utility in the present matter before the Board, namely diagnosing and treating cell proliferation associated disorders such as wound healing associated with oral mucositis for FGF-CX, is fully supported and consistent with generally accepted scientific principles as well as in accordance with current case law.

As shown above, the specification clearly discloses utility of the proteins of this invention for treating ulcers and cells lining the gastrointestinal tract in accordance with the requirement of the patent statutes. As illustrated in the attached Jeffers article (Exhibit 1), the proteins of this invention have a demonstrated therapeutic activity of treating intestinal inflammation in both animal *in vivo* studies and *in vitro* studies using human cell lines. In the scientifically acceptable murine-colitis model, it was shown that prophylactic administration of FGF-CX (corresponding to SEQ ID NO:2 of the claims before the Board) significantly reduced the severity and extent of mucosal damage; in the scientifically accepted rat small bowel ulceration/inflammation model, administration of FGF-CX was shown to reduce small intestinal weight gain, necrosis, inflammation, and weight loss; and in *in vitro* studies it was demonstrated that FGF-CX stimulated cell growth and restitution in human intestinal fibroblast cell lines. Accordingly, FGF-CX (SEQ ID NO:2) has been shown to have a specific, substantial, and credible utility of treating intestinal disorders. This utility was specifically disclosed in the specification as originally filed. Appellants therefore request that the Board withdraw the rejection.

2. Appellants believe that the Examiner's rejection of Claims 1, 5, 41, 46, 63 and 64 under 35 U.S.C. § 112 ¶ 1 (Lack of Enablement) is improper for the following reasons:

Claims 1, 5, 41, 46, 63 and 64 were finally rejected under 35 U.S.C. § 112 ¶ 1 for lack of enablement. This rejection is attendant to the rejection based on the above § 101 lack of utility. Since the Examiner alleges that the claimed invention lacks utility, it follows that one skilled in the art would not know how to use the claimed invention. Appellants do not agree with this determination, and they respectfully request the Board to find in their favor.

The Examiner has implicated a "how to use" utility-based § 112 ¶ 1, rejection. This cannot stand. In order for the Examiner's position to be upheld on the utility-based § 112, ¶ 1, non-enablement rejection, the specific factual showing must represent one of those rare instances meeting the stringent criterion of being "totally incapable of achieving a useful result" Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555 (Fed. Cir. 1992), as discussed in the Legal Analysis accompanying the Utility Guidelines (M.P.E.P. § 2107). The only instances in which the Federal courts have found a lack of patentable utility were where, "based upon the factual record of the case, it was clear that the invention *could and did not work* as the inventor claimed it did." M.P.E.P. § 2107 (emphasis added). These rare cases have been ones in which the applicant either (a) failed to disclose any utility for the invention, or (b) asserted a utility that could be true only "if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.01. That is simply not the case here -- as is evidenced from the Jeffers paper, and the FDA's approval of the IND (Exhibits 1 and 2, respectively).

Appellants have overcome the Office's rejection under § 101 to the claims as amended above. Accordingly, the rejection under § 112, ¶ 1 must also fall. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing comments and reasons, Appellants request that the Board of Patent Appeals and Interferences find in their favor and overturn the Examiner's Final Rejection and return their application to the Examiner with an indication that all claims before the Board in this matter fully comply with the requirements of 35 U.S.C. § 101 and 35 U.S.C. § 112 first paragraph, and are thus in condition for allowance.

Respectfully submitted,

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Dated: July 14, 2003

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PATENT TRADEMARK OFFICE

APPENDIX: CLAIMS ON APPEAL

1. (Previously amended) An isolated polypeptide comprising an amino acid sequence shown in SEQ ID NO:2.

5. (Previously amended) The polypeptide of claim 1, said polypeptide further comprising at least one conservative amino acid substitution, wherein said polypeptide is a full length polypeptide that retains functional growth factor-like properties of SEQ ID NO: 2, retains the conserved amino acids of the FGF family motif located at residues 125, 127, 129, 136, 137, 139, 141 and 148, and retains the hydrophobic transport domain between residues 92-120, wherein the residues are numbered with respect to SEQ ID NO:2.

41. (Previously amended) A composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable carrier.

46. (Previously amended) A kit comprising in one or more containers a composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable carrier.

63. (Previously added) The polypeptide of claim 1, the polypeptide further comprising a post-translational modification other than a proteolytic cleavage.

64. (Previously added) The polypeptide of claim 63, wherein the post-translational modification is at least one modification chosen from the group consisting of phosphorylation and N-myristoylation.